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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MEANS AND METHODS FOR DIAGNOSING AND TREATING AFFECTIVE DISORDERS

(57) Abstract: The present invention relates to nucleic acid molecules, preferably genomic sequences, encoding an ATP-gated ion channel P2X7R which contain a mutation in the 5'UTR or 3'UTR regions, a mutation in exon 3, 5, 6, 8 or 13 or in introns 1, 3, 4, 5, 6, 7, 9, 11 or 12 or a deletion in exon 13, which allow to diagnose affective disorders. The invention further relates to polypeptides encoded by said nucleic acid molecules vectors and host cells comprising said nucleic acid molecules as well as to methods for producing polypeptides encoded by said nucleic acid molecules. The present invention also provides antibodies specifically directed to polypeptides encoded by said nucleic acid molecules and aptamers specifically binding said nucleic acid molecules. Additionally, primers for selectively amplifying said nucleic acid molecules are provided in the present invention as well as kits, compositions, particularly pharmaceutical and diagnostic compositions comprising said nucleic acid molecules, vectors, polypeptides, aptamers, antibodies and/or primers. Moreover, the present invention relates to methods for diagnosing affective disorders associated with a nonfunctional P2X7R protein, an altered ATP-gating of the P2X7R protein, an over- or underexpression of the P2X7R protein or associated with the presence of any one of the aforementioned nucleic acid molecules or polypeptides encoded thereby. Additionally, the present invention relates to uses and methods for treating affective disorders employing a functional or non-functional ATP-gated ion-channel P2X7R. The present invention also relates to uses of modulators of P2X7R activity for treating affective diseases. Furthermore, the present invention also relates to methods for identifying and characterizing compounds which are capable of specifically interacting with or altering the characteristics of the polypeptides of the present invention as well as to methods for the production of pharmaceutical compositions.

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INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C12N15/11 C12N5/10 C12N1/21 C12Q1/68
C07K16/28 A61K31/40 A61K38/17 A61K39/395 A61K31/7088
G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C12Q C07K A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 214 581 B1 (LYNCH KEVIN J ET AL) 10 April 2001 (2001-04-10) column 3 - column 5	36,37, 42-45
X	WO 99/55901 A (ABBOTT LAB) 4 November 1999 (1999-11-04) cited in the application page 3 page 22	36,37, 42-45
A	NORTH R A ET AL: "Pharmacology of cloned P2X receptors." ANNUAL REVIEW OF PHARMACOLOGY AND TOXICOLOGY. 2000, vol. 40, 2000, pages 563-580, XP002304784 ISSN: 0362-1642 cited in the application page 571 - page 572; tables 1,2	

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 November 2004	10. 12. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schneider, P

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SANZ J M ET AL: "TENIDAP ENHANCES P2Z/P2X7 RECEPTOR SIGNALLING IN MACROPHAGES" EUROPEAN JOURNAL OF PHARMACOLOGY, AMSTERDAM, NL, vol. 355, no. 2/3, 1998, pages 235-244, XP001056968 ISSN: 0014-2999 cited in the application the whole document	
A	WO 01/44213 A (BAXTER ANDREW ; ROBERTS BRYAN (GB); KINDON NICHOLAS (GB); THOM STEPHEN) 21 June 2001 (2001-06-21) cited in the application the whole document	
A	EP 1 199 372 A (ASTRAZENECA AB) 24 April 2002 (2002-04-24) page 2 - page 9; claims 1-13 page 15	
A	WO 01/62787 A (OXFORD GLYCOSCIENCES UK LTD ; HERATH HERATH MUDIYANSELAGE AT (GB); PAR) 30 August 2001 (2001-08-30) the whole document	
A	DATABASE EMBL 14 May 1999 (1999-05-14), XP002284283 Database accession no. AC007546 nucleotides 66559-66578 the whole document	
P,X	WO 03/042190 A (PFIZER PROD INC ; DUPLANTIER ALLEN JACOB (US)) 22 May 2003 (2003-05-22) cited in the application page 1 page 25 - page 26	36,37, 42,43,45

INTERNATIONAL SEARCH REPORT

International application No.
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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-12,17-35,40-55 (all partially),36-39,56 (all completely)

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[X] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 24-27 and 54-56 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 30, 34 and 35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: Claims 1-12 and 17-56 (all partially)

nucleic acid molecule comprising a genomic nucleotide sequence according to SEQ ID NO 1 with substitution of nucleotide 362, or fragments containing the substitution, nucleotides hybridizing with the mutated sequence and the use of the nucleic acid molecule in diagnosis and treatment.

Inventions 2-6: Claims 1-12 and 17-56 (all partially)

nucleic acid molecule comprising a genomic nucleotide sequence according to SEQ ID NO 1 with substitution of nucleotide 532, 1100, 1122, 1171, 1702 respectively, fragments containing the substitutions and nucleotides hybridizing with the mutated sequences and their use in diagnosis and treatment of affective diseases.

Inventions 7-13: Claims 1-56 partially

polypeptides according to SEQ 3 or 4 with substitution of amino acid residue 117,150, 186, 191, 270, 568 or 578 respectively, nucleotides or fragments thereof encoding the mutated polypeptide(fragments), nucleotides hybridizing with the mutated nucleotide seqeunce, antibodies against the mutated polypeptide sequence and the use of the polypeptides in diagnosis and treatment of affective diseases.

Inventions 14 and 15: Claims 1-12 and 17-56 (all partially)

nucleic acid molecule comprising a genomic nucleotide sequence according to SEQ ID NO 1 with substitution of nucleotide 32548 or 37633 respectively, fragments containing the substitutions and nucleotides hybridizing with the mutated sequences and the use of the nucleic acid molecules in diagnosis and treatment of affective diseases.

Invention 16: Claims 1-56 partially

polypeptides according to SEQ 3 or 4 with a deletion of amino acids 488-494, nucleotides or fragments thereof encoding the mutated polypeptide(fragments), nucleotides hybridizing with the mutated nucleotide seqeunce, antibodies against the mutated polypeptide sequence and the use of the polypeptides in diagnosis and treatment of affective diseases.

Inventions 17-39: 1-12 and 17-56 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

nucleic acid molecule comprising a genomic nucleotide sequence according to SEQ ID NO 1 with substitution of nucleotides mentioned in claim 1(e) and 1(f) respectively, fragments containing the substitutions and nucleotides hybridizing with the mutated sequences and the use of the nucleic acid molecules in diagnosis and treatment of affective diseases.

Invention 40: 20-27,42-46 (all partially),54-56 completely

Use of P2X7R or its encoding nucleotides or variants thereof as far as not covered by inventions 1-39 in diagnosis of affective disorders

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Invention 41: 20,28-35,40-45,47-53 (all partially),36-39 completely

Use of modulators of P2X7R activity as pharmaceutical against affective disorders as far as not covered by invention 1-40

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